Laterality of Oral Clefts and Academic Achievement

Emily R. Gallagher, MD, MPH,[a] Brent R. Collett, PhD,[b] Sheila Barron, PhD,[c] Paul Romitti, PhD,[d] Timothy Ansley, PhD,[c,e] George L. Wehby, MPH, PhD[f,g]

abstract

BACKGROUND AND OBJECTIVES: Children with isolated oral clefts have lower academic performance when compared with unaffected peers, yet few studies have examined specific attributes of clefts that may modify this risk. Oral clefts have nonrandom laterality, with left-sided clefts being more common than right-sided clefts, a pattern that may be genetically or environmentally influenced. The objective of this study was to evaluate the association between cleft laterality and academic achievement in a population-based sample of children with and without isolated oral clefts.

METHODS: The study included 292 children with isolated unilateral cleft lip with or without cleft palate identified by using the Iowa Registry for Congenital and Inherited Disorders matched with 908 unaffected classmates. This group provided 1953 child-grade observations for cases and 6829 for classmates. Academic achievement was evaluated by using high-quality standardized test data on multiple academic domains as well as use of special education.

RESULTS: We found that children with right-sided clefts had similar achievement scores and usage of special education services compared with their unaffected classmates. Children with left-sided clefts had lower reading scores than children with right-sided clefts by nearly 7 percentiles ($P < .05$). They also had lower scores on all evaluated domains by 4 to 6 percentiles and greater use of special education services by 6 percentage points than their classmates.

CONCLUSIONS: Children with left-sided clefts had poorer academic performance than their classmates or children with right-sided clefts, who showed similar academic achievement compared with their unaffected classmates.

Departments of [a]Pediatrics and [b]Psychiatry and Behavioral Sciences, Child Psychiatry at Seattle Children's Hospital, University of Washington, Seattle, Washington; [c]Iowa Testing Programs, and Departments of [d]Epidemiology, [e]Psychological and Quantitative Foundations, and [f]Health Management and Policy, Economics, and Preventive and Community Dentistry, and Public Policy Center, University of Iowa, Iowa City, Iowa; and [g]National Bureau of Economic Research, Cambridge, Massachusetts

Dr Wehby conceived and designed this study, developed the analysis plan, conducted the analysis, wrote the first version, and critically revised the manuscript; Drs Gallagher and Collett conceived and designed this study, developed the analysis plan, wrote the first version, and critically revised the manuscript; Drs Barron, Romitti, and Ansley contributed to acquiring the data, data interpretation, and critical revisions of the manuscript; and all authors approved the final manuscript.

DOI: 10.1542/peds.2016-2662

Accepted for publication Oct 28, 2016

Address correspondence to George L. Wehby, PhD, National Bureau of Economic Research and Departments of Health Management and Policy, Economics, and Preventive and Community Dentistry, and Public Policy Center, University of Iowa, 145 N. Riverside Dr, 100 College of Public Health Bldg, Rm N250, Iowa City, IA 52242. E-mail: george-wehby@uiowa.edu

WHAT'S KNOWN ON THIS SUBJECT: Children with oral clefts have increased risk for academic deficits and are more likely to receive academic support relative to unaffected peers. Little is known about specific cleft attributes, such as cleft laterality, that may affect risk of learning differences.

WHAT THIS STUDY ADDS: This population-based study examining laterality of clefts showed that patients with typical (left-sided) clefts had lower academic performance compared with peers with atypical (right-sided) clefts or with their unaffected classmates.

To cite: Gallagher ER, Collett BR, Barron S, et al. Laterality of Oral Clefts and Academic Achievement. *Pediatrics.* 2017;139(2):e20162662

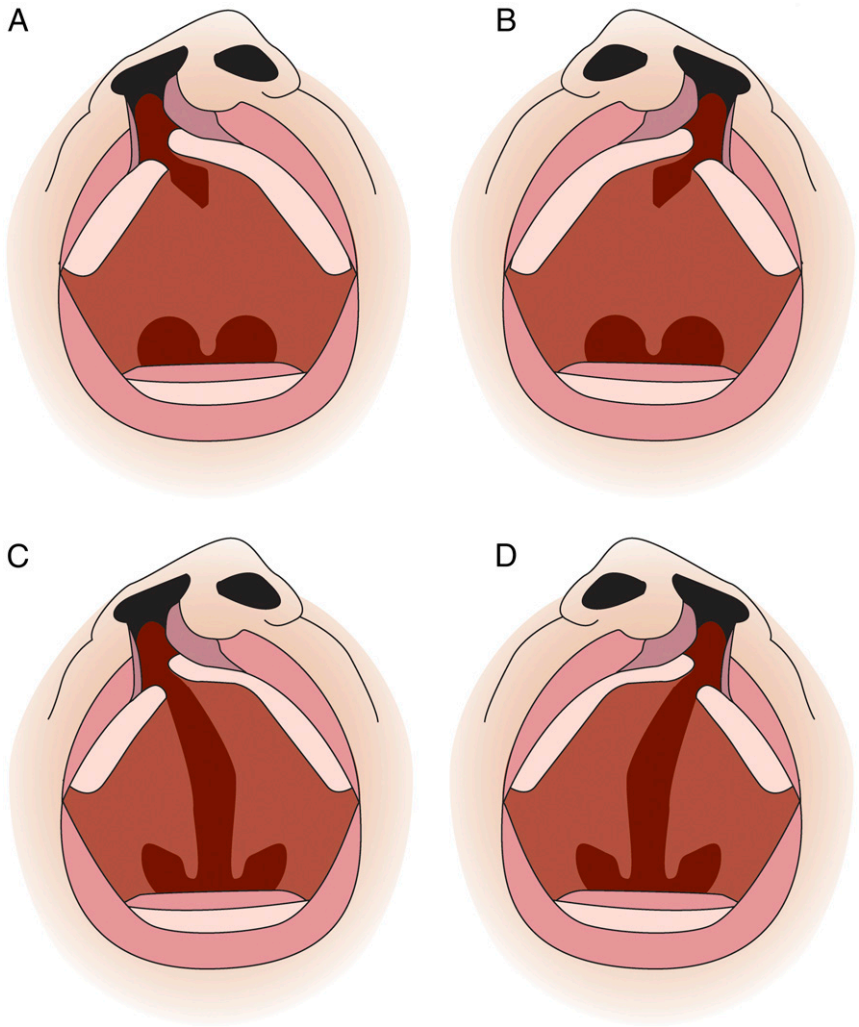

FIGURE 1
Illustration of laterality of oral clefts. A, Right unilateral cleft of the lip and alveolus. B, Left unilateral cleft of the lip and alveolus. C, Right unilateral cleft of the lip and alveolus with cleft palate. D, Left unilateral cleft of the lip and alveolus with cleft palate.[7] © 2012 by John Wiley & Sons, Inc. Used with permission.

Children with isolated oral clefts have been shown to score lower than unaffected classmates on academic achievement measures and are more likely to require academic support relative to unaffected peers.[1–3] Examining differences by cleft type, some studies have reported that academic outcomes are lowest for children with cleft palate only and highest for children with cleft lip only.[4–6] However, a recent large study showed significant deficits for children with oral clefts when compared with unaffected classmates, but no significant differences among cleft types (ie, cleft palate, cleft lip and palate, cleft lip only).[1] Few studies have examined academic or other neurocognitive outcomes in relation to other cleft attributes, such as cleft laterality by comparing right- versus left-sided clefts (Fig 1).

Unilateral clefts of the lip are nearly 2 times as prevalent as bilateral clefts for cases with cleft lip and palate, and just over 10 times as many children with cleft lip only have unilateral versus bilateral clefts.[8] Among those with unilateral clefts of lip (with or without cleft palate), left-sided clefts are twice as common as right-sided clefts for reasons that are not well understood. The more frequent occurrence of unilateral clefts on the left side suggests directional rather than fluctuating asymmetry. Directional asymmetry describes a trait that systematically occurs more often on one side or the other during development. Directional asymmetry may be related to a variety of underlying control processes (eg, genetic variation, environmental insult).[9] In contrast, fluctuating asymmetry describes random variation, in which a trait would be expected to occur with equal frequency on the right or left side. This process suggests nonspecific insults to development. Facial directional asymmetry is also more common among relatives of individuals with unilateral clefts compared with the general population, but not for relatives of individuals with bilateral clefts.[10] It is possible that among multiple genetic pathways controlling facial development, some have fluctuating and some have directional asymmetry.

There are data to suggest that lateralization patterns are related to neurodevelopment.[11] Handedness is often used as an indicator of brain lateralization. Eighty-five percent of humans are right-handed, which implies left-hemisphere dominance.[12] Failure to achieve hand preference and left handedness have been associated with an increased rate of dyslexia and other neurodevelopmental disorders (eg, attention-deficit/hyperactivity disorder[13]). Brandler and Paracchini[14] proposed that this association might reflect a common genetic mechanism that underlies asymmetry in hand preference and brain lateralization. The genes that control cilia formation, which are involved in establishing left/right asymmetry during development, are likely also active in midline brain development and therefore

influence brain dominance and cognitive ability. Similarly, different data sources support that neurodevelopment is tightly linked to facial development.[15] This concept has biologic plausibility because of the shared embryologic origin of the tissues that form the brain and face. Both tissues arise from the prechordal region, then surface ectoderm forms the face and neuroectoderm forms the brain.[16] A relationship may therefore exist between variance in brain lateralization and asymmetric fusion of the facial prominences. This notion is supported by the well-documented finding of a higher preponderance of left handedness seen in patients with oral clefts.[9] Moreover, several studies have shown differences in brain morphology in children with oral clefts compared with controls.[17,18]

A question that remains unanswered is whether the laterality of oral clefts is associated with increased susceptibilities for altered brain functions. This is partly due to the difficulties of enrolling enough individuals with right-sided clefts. To our knowledge, the only study to examine neurodevelopment in relation to cleft laterality was a neuroimaging study by van der Plas et al.[19] In that study, boys with right unilateral clefts were found to have reduced white matter volume compared with boys with clefts on the left side and unaffected controls. Although the sample size used in the study was small and had potential for bias, the findings suggested that there may be additional implications of a cleft lip occurring on the right side versus the left side. Other studies of craniofacial asymmetry and dental anomalies in children with clefts and their relatives have found that such anomalies tend to be largely correlated with the side of the cleft. For craniofacial asymmetry, the side of directional asymmetry within the nasomaxillary complex of the parents highly correlates with the side of the cleft in their affected children.[20] Similarly, dental anomalies in children with clefts occur more often on the same side as the cleft, indicating a local rather than a distant effect.[21]

In this study, we sought to examine the association between cleft laterality and academic achievement in a large, population-based sample of children with isolated cleft lip with/without cleft palate and unaffected classmates. Specifically, we examined whether cleft-sidedness (left or right) among children with unilateral cleft lip (with or without cleft palate) was related to academic achievement. Understanding whether these cleft attributes are associated with academic achievement may provide some insight into the etiology of learning problems in this population.

METHODS

Study Population

The study population has been described previously.[1] The study included 763 children with isolated oral clefts (cases) born to Iowa-resident mothers from January 1983 through December 2003 and their unaffected classmates. Cases were identified from the Iowa Registry for Congenital and Inherited Disorders, which conducts active surveillance of birth defects through field staff who conduct systematic reviews of medical records in hospitals and clinics in Iowa and neighboring states. For this study, we included children with isolated unilateral cleft lip with or without cleft palate (ie, without syndromes or other unrelated major birth defects); children with syndromes that would affect learning were therefore not included. Iowa Registry for Congenital and Inherited Disorders data were linked with data on academic achievement from the Iowa Testing Programs (ITP), described in the following paragraphs, and birth certificate data to measure household demographic factors, by using a process that maintained the anonymity of students to the study researchers. Of the 614 children found in the ITP data set, 468 had cleft lip with/without palate. Of those, 414 had data on laterality, and 292 had unilateral cleft lip. Consistent with previous studies, most cases had left-sided clefts (n = 189, 65%).

Classmates of children with oral clefts were identified from the ITP database. Two classmates were matched for each case by sex, month and year of birth, grade, and school. Matching criteria were relaxed when needed to locate 2 classmates, beginning with month, then year of birth, then school. Classmates were always matched by sex, grade, and school district. When needed (eg, with school switching), additional classmates were selected and matched. We compared affected children to all their matched controls on all grades with available ITP data (before and after switching school districts) to maximize power and eliminate bias from switching schools. Therefore, the classmate sample was more than double that of affected children and included 908 unaffected children, including 596 classmates of children with left-sided clefts and 312 classmates of children with right-sided clefts.

Test scores were linked to each study child (case/classmate) across all of their years in Iowa schools found in ITP data. The sample consisted of child-grade observations, with the child's achievement in each grade as the unit of the analysis. Because all available tests were used for each child (ie, most children were tested more than once), the sample included up to 1953 child-grade observations for the case group and 6829 child-grade observations for classmates, including 4514 observations for classmates of children with left-sided clefts and 2315 child-grade

observations for classmates of children with right-sided clefts.

Academic Achievement

Academic achievement was measured by using the Iowa Tests of Basic Skills for children in kindergarten through eighth grade, and the Iowa Tests of Educational Development for high school students.[22] The Iowa Tests of Basic Skills and Iowa Tests of Educational Development are nationally normed, standardized tests with excellent psychometrics. These tests are administered to virtually all students in Iowa and have been commonly used to test academic achievement in schools across the nation.

We evaluated students' performance in core academic subjects, including reading, language, and mathematics. The primary dependent variables for each testing area and domain were the national percentile rankings (NPRs). In addition to the NPRs, we created a dichotomous score indicating whether the child had an NPR score below the 25th percentile for each of the 3 core areas (reading, language, and mathematics), a commonly used cutoff to identify children in need of academic remediation.[23] We then compared the proportion of cases versus controls with a score <25th percentile for any area (any learning problem), and cases versus controls with scores <25th percentile for all 3 areas combined (multiple learning problems). Finally, we also examined placement in special education (measured beginning in 2001 and every year thereafter) in a given year as an outcome.

Statistical Analysis

We first compared children with right-sided clefts with their own classmates and then children with left-sided clefts with their own classmates. These comparisons allow for controlling for school-level effects. We used linear regression with fixed effects for each child with clefts and his or her own classmates, estimating separate regressions by cleft laterality. Specifically, we estimated a regression for children with right-sided clefts relative to their own classmates that included a binary indicator for having a right-sided cleft versus being an unaffected classmate, and another regression for children with left-sided clefts versus their own classmates that also included a binary indicator for having a left-sided cleft versus a classmate. In all regressions, the child-grade observation was the analysis unit. We adjusted for the following covariates: child grade level, test form used, number of years that the form had been in use, covariates from birth certificate data (parents' marital status, maternal education, paternal education, maternal age, paternal age, maternal race/ethnicity [white, non-Hispanic, or nonwhite or Hispanic]), prenatal tobacco exposure, and prenatal alcohol exposure. Because data on smoking, alcohol, and race/ethnicity were not captured in birth certificates before 1989, and to account for missing data on father's characteristics (>10%), we represented missing data on these variables with dummy variables. We clustered the SEs within groups defined for each affected child and his or her classmates.

To maximize power, we combined cases with cleft lip only and cleft lip with palate in the regressions described previously for examining laterality effects. Because we include an indicator for cleft laterality (versus being a classmate), the regression models described previously could not include 2 additional indicators for cleft type (ie, one for cleft lip only and another for cleft lip with palate). Even though the proportion of left-sided clefts was slightly higher among cases with cleft lip only (68%) versus cases with both cleft lip and palate (61%) in this sample, it is unlikely that cleft type is a confounder in this study because there were generally no significant differences in academic achievement by cleft type in this sample.[1] However, to confirm that there is no bias from cleft type, we reestimated the previously described regressions separately for cases with cleft lip only versus their classmates and then for cases with cleft lip with palate compared with their classmates. Next, for each laterality group, we obtained a weighted average of outcome differences from classmates from the 2 regressions for the 2 cleft types (cleft lip only and cleft lip with palate) by using the proportions of the number of observations in each regression relative to the total sample as weights. Because this estimation was stratified by cleft type, the estimated differences by cleft-sidedness from classmates were not biased by cleft type. Because SEs of this weighted estimate are not directly obtained, we focused on comparing the magnitude of the weighted estimates with the main estimates rather than on their statistical significance.

In addition to the analyses specific to each laterality group compared with their classmates, we directly compared children with left-sided clefts with those with right-sided clefts. We adjusted for similar covariates in addition to cleft type and binary indicators for birth period. SEs were clustered at the child level.

RESULTS

Outcome Description

Descriptive statistics for all outcomes are summarized by group in Table 1. Children with left-sided clefts had the lowest scores on reading on average and the highest rate of using special education than the other groups. Language scores were comparable on average by cleft laterality. Group score averages ranged from nearly 56 to 62 percentiles. The classmate group for children with left-sided

TABLE 1 Outcome Summaries by Cleft Laterality and Affected/Unaffected Status

	Children With Right-Sided Clefts Versus Classmates		Children With Left-Sided Clefts Versus Classmates	
	Children With Clefts	Classmates	Children With Clefts	Classmates
Reading, mean (SD)	59.5 (27.0)	57.0 (28.5)	55.7 (28.0)	58.2 (27.3)
Language, mean (SD)	55.7 (29.2)	57.0 (28.2)	55.9 (28.2)	59.2 (27.2)
Mathematics, mean (SD)	58.0 (27.6)	60.9 (28.0)	59.6 (27.5)	61.8 (27.4)
Reading, language, or math scores < national 25th percentile, %	15.5	16.4	15.1	13.3
Reading, language, and math scores < national 25th percentile, %	5.5	7.8	6.8	5.9
Special education, %	16.3	17.6	18.9	13.8

The sample size for the summary statistics ranged from 412 to 645 child-grade observations for children with right-sided clefts, from 810 to 1189 child-grade observations for children with left-sided clefts, from 1380 to 2194 child-grade observations for classmates of children with right-sided clefts, and from 2764 to 4245 child-grade observations for classmates of children with left-sided clefts. The smallest sample size was for special education (first measured in 2001) and largest for mathematics scores. There were no statistically significant differences in outcomes between the 2 classmate groups based on comparisons in unadjusted regressions or those adjusted for the same covariates as in the main models.

TABLE 2 Differences in Educational Achievement by Cleft Laterality Compared With Classmates

	Reading	Language	Mathematics	Reading, Language, or Mathematics <25th Percentile	Reading, Language, and Mathematics <25th Percentile	Special Education
A. Children with right-sided clefts versus their own classmates						
β (SE)	2.22 (3.35)	−1.81 (3.46)	−2.89 (2.95)	−0.009 (0.032)	−0.024 (0.020)	−0.008 (0.052)
B. Children with left-sided clefts versus their own classmates						
β (SE)	−4.70** (2.11)	−5.70*** (1.96)	−3.78** (1.89)	0.047* (0.025)	0.029*(0.016)	0.061** (0.031)

A separate regression is estimated for each academic achievement outcome and for each laterality group compared with their corresponding classmates. The regression coefficient (β) indicates how the scores of children with clefts compare with those of their classmates. For example, the β of −4.70 (under reading) indicates that children with left-sided clefts have lower scores on reading than their classmates by 4.70 percentiles on average. SEs of the βs are in parentheses. The regressions control for fixed effects for each child with clefts and his or her own classmates, grade level, test form, number of years since the form was used, and household sociodemographic factors. For children with right-sided clefts versus their classmates, the sample size for the regressions ranged from 1783 (special education) to 2830 (mathematics) child-grade observations. For children with left-sided clefts, the sample size ranged from 3564 (special education) to 5424 (mathematics) child-grade observations.

* $P < .1$;

** $P < .05$;

*** $P < .01$.

clefts had consistently better achievement outcomes than the classmate group for children with right-sided clefts, although none of these differences was statistically significant. Such differences may occur because of variation in geographic location and school or area-level effects. There were no sociodemographic differences among children with clefts by cleft laterality (Supplemental Table 4).

Differences in Academic Achievement Between Each Cleft Laterality Group and Classmates

Scores were similar for children with right-sided clefts and their classmates for all outcomes, with no statistically significant differences observed (Table 2). In contrast, children with left-sided clefts had significantly lower average scores on reading, language, and mathematics than their corresponding classmates by ∼5, 6, and 4 percentiles, respectively. Their scores were also more likely to be <25th percentile on either domain and on all 3 domains, suggesting greater risk of learning problems. These children were also more likely to use special education services by ∼6 percentage points. Accounting for cleft type (cleft lip only versus cleft lip with palate) provided similar results (Supplemental Table 5).

Differences in Academic Achievement Between the Cleft Laterality Groups

Table 3 reports the results of the regressions comparing the academic achievement of children with left-sided clefts directly with those with right-sided clefts (ie, not compared with their classmates). Children with left-sided clefts had generally lower achievement than children with right-sided clefts. The only significant difference, however, was for reading, with children with left-sided clefts having lower scores by nearly 7 percentiles on average.

DISCUSSION

Children with left-sided clefts scored lower than their classmates on all domains and were more likely to use special education services. They also had a marginally significant increase in risk of learning problems (any or

TABLE 3 Differences in Educational Achievement Between Children With Left-Sided Clefts and Those With Right-Sided Clefts

	Reading	Language	Mathematics	Reading, Language, or Mathematics <25th Percentile	Reading, Language, and Mathematics <25th Percentile	Special Education
β (SE)	−6.62** (3.30)	−3.40 (3.32)	−1.10 (3.01)	0.043 (0.036)	0.034 (0.021)	0.042 (0.049)

A separate regression is estimated for each academic achievement outcome comparing children with left-sided clefts directly with children with right-sided clefts. The regression coefficient (β) indicates how the scores of children with left-sided clefts compare with those with right-sided clefts. For example, the β of −6.62 (under reading) indicates that children with cleft-sided clefts have lower scores on reading than children with right-sided clefts by 6.62 percentiles on average. SEs of the βs are in parentheses. The regressions control for cleft type (cleft lip only versus cleft lip with palate), sex, binary indicators for birth period (1986–1989, 1990–1994, 1995–1999, and 2000–2003, with 1983–1985 as the reference category), grade level, test form, number of years since the form was used, and household sociodemographic factors as covariates. The sample size for the regressions ranged from 1216 to 1828 child-grade observations.

** $P < .05$.

multiple). In contrast, there were no statistically significant differences between children with right-sided clefts and their classmates. When comparing children with clefts by laterality directly, children with left-sided clefts had lower reading scores on average than children with right-sided clefts. These findings suggest that children with the more common left-sided clefts may face higher learning and neurodevelopmental risks than children with atypical right-sided clefts. These results are in contrast to a study by van der Plas et al,[19] which showed reduced white matter in children with right-sided clefts relative to those with left-sided clefts and unaffected controls.

Despite potential differences by laterality, our findings should not be interpreted as ruling out the need to screen all children with isolated unilateral cleft lip with/without palate. Children with right-sided clefts had slightly lower language and mathematics scores than their classmates, and the differences may have been statistically nonsignificant because of the smaller sample size compared with children with left-sided clefts. The findings of lower performance scores in the subgroup of children with left-sided clefts, as has been shown previously for the full cohort of patients with oral clefts,[1] supports the finding that children with oral clefts are at greater risk of poor academic performance and should be screened appropriately.

Several studies[9,24,25] have shown that children with cleft lip with or without cleft palate are more likely to be left-handed compared with children without oral clefts. This finding is thought to be related to the common embryologic origin of the face and brain (neural ectoderm), in which asymmetric fusion of the facial prominences also may be associated with brain lateralization. However, a clear association between cleft laterality and non–right-handedness has not been established. Further studies looking at whether atypical patterns of laterality with both oral clefts and hemispheric dominance are associated may help explain these findings. Furthermore, studies looking at cleft severity (ie, width of the cleft lip, alveolus, or palate) as it correlates to academic outcomes are lacking and were not addressed in this analysis. It is also possible that health care providers may be somewhat biased in providing more intensive care or follow-up to children with the less common right-sided clefts because of the assumption that they may be at greater risk of developmental delay. However, we have no data on the health care services that these children received to test this hypothesis.

Recurrence and genetic studies have suggested that the occurrence of isolated oral clefts may be partly explained by a multifactorial threshold model.[26] This model implies that both environmental and genetic factors can alter the risk of developing a cleft, which occurs when risk exceeds a certain threshold. This also suggests that less common traits, such as right-sided clefts, may have higher risk thresholds and thus possibly more severe forms because they may involve more intense genetic or environmental risk factors.[27] However, the premise of increased severity of right-sided clefts was not evident in this study when examining academic outcomes.

A strength of this investigation is the large cohort and population-based sampling, which allowed comparison of children with left- versus right-sided clefts with their unaffected classmates, as well as to the other laterality subgroup. This controlled for differences resulting from quality of schools and classroom instruction, as well as for socioeconomic confounders. Using a well-established standardized test covering key subject areas also strengthened the depth of the analysis and allowed for comparison of different academic areas.

A potential limitation of this study was the inclusion of only children with isolated oral clefts. This did not allow for comparison of children with clefts associated with genetic syndromes or those with other major anomalies. Czeizel et al[28] suggested that the increased frequency of left-sided clefts is not observed in syndromic forms of clefting. Therefore, our findings may not necessarily apply to nonisolated cases. Another potential limitation is the missing data on laterality for some patients (54 of 414, 13%) who were therefore not included in the analysis.

CONCLUSIONS

Among children with isolated unilateral cleft lip (with or without cleft palate), children with the more typical left-sided clefts scored lower on academic performance measures when compared with classmates or with children with right-sided clefts. Health care providers should screen all children with oral clefts for risk of developmental or academic problems. Further studies will help delineate whether cleft laterality can be used to better understand distinct developmental pathways and exposures that may increase the risk of poor academic outcomes.

ACKNOWLEDGMENTS

The authors thank Dr Lina Moreno Uribe, associate professor at the Department of Orthodontics and Dows Research Institute, College of Dentistry, University of Iowa, Iowa City, Iowa, for critical review of the article and for helpful suggestions. The authors also thank Eden Palmer and Erik Stuhaug for their assistance on the drawings shown in Fig 1.

ABBREVIATIONS

ITP: Iowa Testing Programs
NPR: national percentile ranking

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The study was funded by grant 1 R03 DE022094 from the National Institutes of Health, National Institute of Dental and Craniofacial Research (NIDCR). Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Wehby GL, Collet B, Barron S, Romitti PA, Ansley TN, Speltz M. Academic achievement of children and adolescents with oral clefts. *Pediatrics*. 2014:133(5):785–792
2. Yazdy MM, Autry AR, Honein MA, Frias JL. Use of special education services by children with orofacial clefts. *Birth Defects Res A Clin Mol Teratol*. 2008;82(3):147–154
3. Knight J, Cassell CH, Meyer RE, Strauss RP. Academic outcomes of children with isolated orofacial clefts compared with children without a major birth defect. *Cleft Palate Craniofac J*. 2015;52(3):259–268
4. Collett BR, Leroux B, Speltz ML. Language and early reading among children with orofacial clefts. *Cleft Palate Craniofac J*. 2010;47(3):284–292
5. Persson M, Becker M, Svensson H. Academic achievement in individuals with cleft: a population-based register study. *Cleft Palate Craniofac J*. 2012;49(2):153–159
6. Broder HL, Richman LC, Matheson PB. Learning disability, school achievement, and grade retention among children with cleft: a two-center study. *Cleft Palate Craniofac J*. 1998;35(2):127–131
7. Gallagher ER, Berg J. Clinical correlate: cleft lip and palate. In: McCauley LK, Somerman MJ, eds. *Mineralized Tissues in Oral and Craniofacial Science: Biological Principles and Clinical Correlates*. Ames, IA: Wiley-Blackwell; 2012
8. Genisca AE, Frías JL, Broussard CS, et al; National Birth Defects Prevention Study. Orofacial clefts in the national birth defects prevention study, 1997–2004. *Am J Med Genet A*. 2009;149A(6):1149–1158
9. Weinberg SM, Neiswanger K, Martin RA, et al. The Pittsburgh Oral-Facial Cleft study: expanding the cleft phenotype. Background and justification. *Cleft Palate Craniofac J*. 2006;43(1):7–20
10. Miller SF, Weinberg SM, Nidey NL, et al. Exploratory genotype-phenotype correlations of facial form and asymmetry in unaffected relatives of children with non-syndromic cleft lip and/or palate. *J Anat*. 2014;224(6):688–709
11. Nelson EL, Campbell JM, Michel GF. Early handedness in infancy predicts language ability in toddlers. *Dev Psychol*. 2014;50(3):809–814
12. Marchant L, McGrew W. Human handedness: an ethological perspective. *Hum Evol*. 1998;13(3–4):221–228
13. Fagard J. Early development of hand preference and language lateralization: are they linked, and if so, how? *Dev Psychobiol*. 2013;55(6):596–607
14. Brandler WM, Paracchini S. The genetic relationship between handedness and neurodevelopmental disorders. *Trends Mol Med*. 2014;20(2):83–90
15. Kjaer I. Human prenatal craniofacial development related to brain development under normal and pathologic conditions. *Acta Odontol Scand*. 1995;53(3):135–143
16. Helms JA, Cordero D, Tapadia MD. New insights into craniofacial morphogenesis. *Development*. 2005;132(5):851–861
17. Adamson CL, Anderson VA, Nopoulos P, Seal ML, Da Costa AC. Regional brain morphometric characteristics of nonsyndromic cleft lip and palate. *Dev Neurosci*. 2014;36(6):490–498

18. Chollet MB, DeLeon VB, Conrad AL, Nopoulos P. Morphometric analysis of brain shape in children with nonsyndromic cleft lip and/or palate. *J Child Neurol*. 2014;29(12):1616–1625

19. van der Plas E, Conrad A, Canady J, Richman L, Nopoulos P. Effects of unilateral clefts on brain structure. *Arch Pediatr Adolesc Med*. 2010;164(8):763–768

20. Yoon Y-J, Perkiomaki MR, Tallents RH, et al. Association of nasomaxillary asymmetry in children with unilateral cleft lip and palate and their parents. *Cleft Palate Craniofac J*. 2003;40(5):493–497

21. Howe BJ, Cooper ME, Vieira AR, et al. Spectrum of dental phenotypes in nonsyndromic orofacial clefting. *J Dent Res*. 2015;94(7):905–912

22. Hoover H, Dunbar S, Frisbie D, et al. *Iowa Test of Basic Skills Guide to Research and Development*. Itasca, IL: The Riverside Publishing Company; 2003

23. Fletcher JM, Francis DJ, Morris RD, Lyon GR. Evidence-based assessment of learning disabilities in children and adolescents. *J Clin Child Adolesc Psychol*. 2005;34(3):506–522

24. Jeffery SL, Boorman JG. Left or right hand dominance in children with cleft lip and palate. *Br J Plast Surg*. 2000;53(6):477–478

25. Scott NM, Weinberg SM, Neiswanger K, Brandon CA, Marazita ML. Hair whorls and handedness: informative phenotypic markers in nonsyndromic cleft lip with or without cleft palate (NS CL/P) cases and their unaffected relatives. *Am J Med Genet A*. 2005;136(2):158–161

26. Grosen D, Chevrier C, Skytthe A, et al. A cohort study of recurrence patterns among more than 54,000 relatives of oral cleft cases in Denmark: support for the multifactorial threshold model of inheritance. *J Med Genet*. 2010;47(3):162–168

27. Firth HV, Hurst JA, Hall JG. *Oxford Desk Reference: Clinical Genetics*. New York, NY: Oxford University Press; 2005

28. Czeizel E, Telegdi L, Tusnády G. *Multiple Congenital Abnormalities*. Budapest, Hungary: Akadémiai Kiadó; 1988

Laterality of Oral Clefts and Academic Achievement

Emily R. Gallagher, Brent R. Collett, Sheila Barron, Paul Romitti, Timothy Ansley and George L. Wehby

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-2662 originally published online January 4, 2017;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Laterality of Oral Clefts and Academic Achievement

Emily R. Gallagher, Brent R. Collett, Sheila Barron, Paul Romitti, Timothy Ansley and George L. Wehby

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-2662 originally published online January 4, 2017;